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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,455	HOUGHTON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-36 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment

Applicant's Preliminary Amendment filed, July 27, 2001, cancels the original claims 1-26 and presents the new claims 27-36. Claims 27-30 are drawn to compositions that comprise hepatitis C virus polypeptides comprising, in claim 27, part of the hepatitis C virus NS3 protein designated a protease at pages 6-8 of the specification – an amino-terminal region of the overall NS3 protein, and, in claims 28-30, compositions that comprise "active" proteases that are truncation analogs including amino acid sequences of, variously, the undecapeptide of SEQ ID NO: 63, or the nonapeptide of SEQ ID NO:64, or the 202-amino acid protein of SEQ ID NO:65 which includes both of SEQ IDs NOs:63 and 64. Claims 31 and 33-35 are drawn to compositions comprising hepatitis C virus polypeptides that are fusion polypeptides joining one of the regions described in claims 27-30 with an undesignated "fusion partner", and claim 33 indicates that human superoxide dismutase is a specific fusion partner. Finally, claim 36 is drawn to an assay for finding a compound that acts against the hepatitis C virus as whole by placing one of the polypeptides, described by claims 27-30 as present within compositions, in contact with candidate inhibitor compounds to measure which will inhibit the "proteolytic activity" of a "hepatitis C virus polypeptide". No pending claim excludes the presence in the polypeptides of the compositions of a region that is a distant part of the initial hepatitis C virus translation product, termed a polyprotein at page 5 of the specification, together with the NS3 protein region the specification states is a protease. Even a composition of claim 32, which comports with a definitional statement at page 10 of the specification indicating that a "fusion partner" is a non-HCV protein, permits a hepatitis C virus polypeptide of claim 31 from which it depends to include more than the amino-terminal region of the NS3 protein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,585,258. Although the conflicting claims are not identical, they are not patentably distinct from each other because a composition comprising a "purified" protease of any of claims 27-30 herein is indistinguishable from compositions comprising proteases of the patented claims 1-4.

Claims 31-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-9 of U.S. Patent No. 5,585,258 in view of in view of Benson et al., U.S Patent No. 5,258,496. Although the conflicting claims are not identical, they are not patentably distinct from each other because a composition comprising a fusion polypeptide that joins an hepatitis C virus protease to another polypeptide according to claims 27-30 herein is obvious over the recombinantly-produced fusion polypeptides of the patented claims 5-9 in view of the teaching of Benson et al. that recombinantly-produced fusion polypeptides are ordinarily comprised in compositions during purification from a host cell wherein they are expressed.

Claim 36 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-5 of U.S. Patent No. 5,597,691. Although the conflicting claims are not identical, they are not patentably distinct from each other because the assay method of claim 36 herein is practiced with a "purified" protease of either of claims 27-30 herein which comprise the amino acid sequence regions required for proteases used in the otherwise corresponding assay methods of the patented claims 1 and 3-5.

Claims 27 and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,712,145. Although the conflicting claims are not identical, they are not patentably distinct from each other because a composition comprising a "purified" protease of either of claims 27 and 30 herein comprises a protease having the amino acid sequence regions necessary for proteolytic activity present in protease amino acid sequences required by claim limitations of compositions of the patented claims 1 and 2.

Claims 31, 32 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 of U.S. Patent No. 5,712,145 in view of Benson et al., U.S Patent No. 5,258,496. Although the conflicting claims are not identical, they are not patentably distinct from each other because a composition comprising a fusion polypeptide that joins an hepatitis C virus protease to another polypeptide according to claims 31, 32 and 35 herein is obvious over the recombinantly-produced fusion polypeptides of the patented claims 3-5 in view of the teaching of Benson et al. that recombinantly-produced fusion polypeptides are ordinarily comprised in compositions during purification from a host cell wherein they are expressed.

Claim 36 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 8 of U.S. Patent No. 5,712,145. Although the conflicting claims are not identical, they are not patentably distinct from each other because the assay method of claim 36 herein is practiced with a "purified" protease of either of claims 27 and 30 herein comprises a protease having the amino acid sequence regions necessary for proteolytic activity present in the protease amino acid sequences required by claim limitations of the patented claims 7 and 8 to otherwise corresponding assay methods.

The following are <u>provisional</u> obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 27 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 of copending Application No. 10/409,094, which is an application for reissue of U.S. Patent No. 5,585,258. Although the conflicting claims are not identical, they are not patentably distinct from each other because compositions of claims 27 and 39 herein comprise

proteases having an amino acid sequence region providing proteolytic activity present in a protease amino acid sequence required by claim 11 of the copending application.

Claim 36 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/409,673, which is an application for reissue of U.S. Patent No. 5,597,691. Although the conflicting claims are not identical, they are not patentably distinct from each other because the assay method of claim 36 herein is practiced with a "purified" protease of either of claims 27 and 30 herein which comprise an amino acid sequence region required in a protease consisting of SEQ ID NO:65 used in the otherwise corresponding assay method of claim 6 of the copending application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 31, and 36 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the proteolytic polypeptides of compositions of claims 27 and 31 which recite no structural feature of a claimed "proteolytic hepatitis C virus polypeptide", and fails to exemplify or describe the practice of a method of claim 36, which depends from claims 27 and 31 which recite no structural feature of a claimed "proteolytic hepatitis C virus polypeptide", because the specification fails to identify an amino acid sequence that constitutes a proteolytic hepatitis C virus polypeptide comprising a generic NS3 domain protease meeting the definition at page 6 of the specification, "an enzyme derived from HCV which exhibits proteolytic activity . . . encoded in the NS3 domain of the HCV genome". In addition, the specification fails to exemplify or describe purification of a "proteolytic hepatitis C virus polypeptide", or to exemplify or describe purification of a "proteolytic hepatitis C virus

polypeptide" further comprising a fusion protein, that would support the preparation of claimed compositions comprising such "purified" proteolytic polypeptides. Nothing in the specification indicates that at the time application serial No. 07/680,296 – the first to provide the disclosure of the instant application – was filed on April 4, 1991, Applicant possessed a polypeptide encoded by any particular region of the HCV genome, or possessed a fusion polypeptide comprising a polypeptide encoded by a particular region of the HCV genome, that could recognize and cleave a particular substrate, whether a peptide or polypeptide comprising an amino sequence set forth at page 21, lines 13-15, of the specification or some other substrate. The results that Example 5 suggests at pages 31 and 32 of the specification cannot be shown to have been caused by a proteolytic activity of a hepatitis C virus-encoded protein, or domain, present in Applicant's particular fusion protein expressed in *E. coli* host cells where it failed to include a peptide sequence actually recognized and cleaved by as much of the NS3 domain "protease" the fusion polypeptide comprised, thus products detected by ELISA in that Example can only be produced by the activity of endogenous host cell proteases.

Similarly, no "purified proteolytic HCV polypeptide" of claim 36 described by claims 27 and 31 is shown to cleave any "peptide substrate" in a control assay so that a baseline of proteolytic activity could be established with which to practice a method of claim 36. The specification does not otherwise show that Applicant had prepared a proteolytic HCV polypeptide that could cleave any particular viral or peptide substrate where the disclosure of Example 6 is hypothetical in its description of the recovery of an active protease and the disclosures of Examples 8-10 are hypothetical in their descriptions of the expression of an active protease in yeast cells or in an *in vitro* transcription and translation system. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe

that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification nowhere furnishes relevant identifying characteristics of a proteolytic hepatitis C virus protease, or fusion protein, encoded by polynucleotide of a claimed composition, or encoded by a claimed expression vector, that can cleave or proteolytically process an hepatitis C virus polyprotein, or any portion thereof, or any other particular polypeptide peptide. Indeed, the subsequent disclosures of Tomei et al., 1994, Lin et al., 1994, De Francesco et al., 1996, Ramanathan et al. 1996, Lin et al., 1997, and Thomson et al., 1997, made record herewith, indicate the contrary: that another region, termed the NS4A cofactor, in the hepatitis C virus polyprotein, a region not encoded by a nucleic acid sequence in any of Applicant's expression vectors of Examples 5-11, must be present together with the NS3 protein's amino-proximal region in order to produce proteolytic activity specific to an hepatitis C virus protease.

Claims 27-36 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for recombinant expression of a catalytic component of a hepatitis C virus protease comprising the amino acid sequence set forth in SEQ ID NO:66, does not reasonably provide enablement for preparation of compositions, or expression vectors, that comprise polynucleotides encoding a proteolytically active hepatitis C virus protease, whether or not fused to a fusion partner. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Although the specification identifies, e.g., in the amino acid sequence of SEQ ID NO:66, a region in the hepatitis C virus NS3 protein with sequence characteristics of a serine protease and makes the appropriate analogies between the hepatitis C virus NS3 product and proteolytic products located in analogous regions of polyproteins encoded by the RNA genomes of other flaviviruses, it provides no guidance for the preparation of claimed compositions comprising polypeptides, or fusion proteins, capable of the proteolytic processing of a hepatitis C virus polyprotein. This is because the

specification does not describe, thus cannot enable, an integral hepatitis C virus protease capable of cleaving a defined substrate. In addition, the small peptides indicated in claims 28, 29, 33 and 34 are insufficient to support proteolysis even if Applicant's disclosure had provided guidance for finding regions of the polyprotein encoded by the hepatitis C virus genome that could provide specificity.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying factors stated in *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)). Applying the enablement analysis discussed in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for determining those portions of the hepatitis C virus polyprotein amino acid sequences that provide specific recognition of the native cleavage sites in the polyprotein,

b) the specification lacks working examples wherein any composition described by claims 27-35 is shown to properly recognize and cleave any portion of the hepatitis C virus polyprotein, or a peptide substrate based on the predicted cleavage sites, and,

c) in view of the publications made of record herein, the state of the art and level of skill in the art at the time the instant disclosure was first filed do not support the identification of other, distant, regions of flavivirus or hepatitis C virus translation products that confer proper cleavage specificity.

Thus the scope of the claimed subject matter cannot be considered to be supported by the disclosure of the present specification.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-36 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27 and 31 are indefinite in reciting, "proteolytic hepatitis C virus polypeptide . . . compris[ing] an HCV NS3 domain protease or an active . . . truncation analog", because the specification does not provide a specific, limiting, structural description of a generic NS3 domain protease thus the public and the artisan attempting to establish the scope of the claimed subject matter could not determine what is more than the protease and what is a truncation analog of the protease, thus could not determine the metes and bounds of the intended subject matter.

Claims 27-35 are indefinite because claims 27 and 31, from which claims 28-30 and 32-35 depend, recite "[a] composition comprising a purified . . . polypeptide" where no polypeptide can remain a "purified" polypeptide when present in a composition. Claim 36 is likewise indefinite because clause (a) recites, "providing a purified . . . polypeptide according to . . . claims 27-35", and clauses (b) and (c) recite "said purified . . . polypeptide", yet claims 27-35 cannot describe a purified proteolytic HCV polypeptide and do not provide for purification of proteolytic HCV polypeptides. Thus the public and the artisan cannot determine the meets and bounds of the intended subject matters.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 27-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miyamura et al., U.S. 5,372,928, in view of Miller et al., 1990, Proceedings of the National Academy of Sciences, U.S.A., Vol. 87, pages 2057-2061, Bazan et al., 1989, Virology, Vol. 171, pages 637-639, and Gorbalenya et al., 1989, Nucleic Acids Research, Vol. 17, pages 3889-3897, all made of record herewith.

For purposes of this rejection, the recitation in claim 27 of "purified" is given no effect because polypeptides within compositions can no longer be considered "purified", and the recitation in claim 27, "composition comprising a . . . polypeptide compris[ing . . .] an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog", is construed as describing compositions comprising polypeptides that need not be the initially translated hepatitis C virus polyprotein but that comprise at least a portion of its NS3 domain.

Miyamura et al. is available herein under 35 U.S.C. § 102(e) as prior art to claims 27-35 in view of the September 15, 1989, filing date of their priority application serial No. 07/408,045, which discloses the portions of their patent this rejection relies on. Miyamura et al. teach a polynucleotide encoding the polyprotein of the hepatitis C virus 1 strain in Figures 12A-C and also teach the relative positions of the structural and the non-structural domains within the hepatitis C virus 1 polyprotein wherein the "putative NS3 [domain extends] from about amino acid 1007 to about amino acid 1650". See, cols. 6-7 and Figure 11, and particularly col. 7 at lines 8-10. Miyamura et al. need not teach an amino acid sequence in Figures 12A-C because determining the amino acid sequence of the encoded polyprotein would have been routine in the art at the time the invention was made and the polyprotein amino acid sequence was indeed disclosed in the priority application serial No. 07/408,045. Miyamura et al. also teach that functions of domains within the hepatitis C virus polyprotein may be predicted on the basis of similarities shared by the amino acid sequences of flaviviruses and the hepatitis C virus

amino acid sequence and that a protease function resides in the amino acid sequences of flavivirus NS3 domains. See col. 17 at lines 5-21. These teachings have priority to September 15, 1989, when they appeared in the parent application serial No. 07/408,045. While Miyamura et al. do not teach how to identify an amino acid sequence region with a protease function and are silent about the presence or absence of other viral functions residing in the NS3 domain of a flavivirus or hepatitis C virus polyprotein, they teach preparation of cloning vectors, and transformed host cells comprising the vectors, comprising inserts of specific, defined, regions found anywhere in a nucleic acid sequence encoding all or part of an hepatitis C virus polyprotein in Examples I-IV at cols. 28-39. Miyamura et al. explicitly teach, at cols. 8-10, that expression vectors comprising transcriptional and translational regulatory elements operably linked to a polynucleotide encoding a desired regions of the hepatitis C virus polyprotein should be used to produce desired portions of the hepatitis C virus polyprotein in host cells, and further suggest preparation of expression constructs providing fusions of hepatitis C virus amino acid sequence regions with proteins commonly used in the art as fusion partners such as β-galactosidase and superoxide dismutase [SOD]. See, col. 14, line 41, through col. 15, line 14.

Miller et al. teach, Figure 2, the identification of the amino acid sequence of the helicase region within the NS3 domain of an hepatitis C virus polyprotein, relying upon the disclosure of Houghton et al. ('216) and comparisons with flavivirus helicase amino acid sequences. Miller et al. specifically teach, at page 2060, right column, that three conserved peptide regions allow them to align a 190-amino acid sequence disclosed in EP 0318216, but not identified therein as a helicase domain, with NS3 domain helicase regions of a flavivirus and a plant potyvirus. Bazan et al., 1989, teach that the amino-terminal third of the NS3 domains of flavivirus polyproteins comprise a serine protease

region having sequence homology with cellular serine proteases, and that a helicase amino acid sequence region is characteristically present in NS3 domains of flavivirus polyproteins carboxyl-proximal to the protease region. Bazan et al., 1989, specifically teach, see, e.g., Figure 1 and its legend, that proposed flavivirus and pestivirus protease regions have particularly conserved amino acid sequences in the immediate vicinity of the residues of the catalytic triad – histidine, aspartate and serine – of a serine protease and that distances between these three catalytic amino acids are uniformly conserved in the primary structures of the protease regions among the flaviviruses. Bazan et al. additionally teach, at page 637, that flavivirus proteases probably cleave amino acid sequences after pairs of basic amino acids. Gorbalenya et al. similarly teach that flaviviruses and pestiviruses have protease regions in the amino-terminal portions of NS3 domains, that amino acid sequences in the immediate vicinity of residues of the catalytic triad are particularly conserved, and that the distances between the three catalytic amino acids are uniformly conserved in primary structures of protease regions among flaviviruses. See Figure 1 and its legend. Gorbalenya et al. further teach, at page 3889, that these proteases "are probably involved in the processing of the viral non-structural proteins."

In view of the teachings of Miyamura et al. that the functions of the domains within the hepatitis C virus polyprotein may be predicted on the basis of similarities shared by the amino acid sequences of flaviviruses and hepatitis C virus and that a protease function resides in the amino acid sequence of flavivirus NS3 domains, as well as their structural teachings of the entire coding sequence for an hepatitis C virus polyprotein and the amino positions of the encoded amino acid sequence that are the boundaries of the NS3 domain in hepatitis C virus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to translate the polyprotein encoded by the

DNA sequence of Figure 12 of Miyamura et al., compare the consensus flavivirus protease amino acid sequences of Bazan et al. and Gorbalenya et al. with the amino-proximal region of the hepatitis C virus NS3 domain having the boundaries taught by Miyamura et al., and prepare a polynucleotide encoding only an hepatitis C virus protease in order to insert it in an expression vector, or within a vector providing a fusion construct, to then produce the protease or fusion protein. The instant specification discloses no purification of claimed protease polypeptides or fusion polypeptides, thus combination of teachings of Miyamura et al., Bazan et al., and Gorbalenya et al. renders obvious subject matter commensurate with the scope of the instant specification.

This is because both Bazan et al. and Gorbalenya et al. agree on structural features that can identify key amino acid sequence regions of NS3 domain proteases of flaviviruses and because Miyamura et al. teach that amino acid sequences of flaviviruses are predictive of structures and features of hepatitis C virus amino acid sequences and also teach how to prepare polynucleotide coding sequences from anywhere within the hepatitis C virus genome in order to insert them in expression vectors and fusion constructs to recombinantly produce the encoded region. Such an artisan would have been motivated to do so because Gorbalenya et al. teach that NS3 domain proteases are probably involved in processing of the viral non-structural proteins, thus integral to the infection process. Such an artisan would have had a reasonable expectation of success in applying the teachings of Gorbalenya et al. and Bazan et al. to identify a polynucleotide of Figure 12 of Miyamura et al. that encodes a protease comprising the amino-terminal region of the NS3 domain because Miller et al. successfully used amino acid sequence comparison of flavivirus and hepatitis C virus to identify the helicase region in the carboxyl terminus of the hepatitis C virus NS3 domain.

Miyamura et al. is available as prior art under 35 U.S.C. § 102(e) because it is the work of another and because its parent application 07/408,045 provides a priority date of September 15, 1989, in its Figures 6-1 through 6-9, including the deduced amino acid sequence, for the disclosure of Figures 12A-C. Miller et al., Bazan et al., and Gorbalenya et al. are available as prior art under 35 U.S.C. § 102(a) because they were published within a year of the relevant date of April 4, 1990. Thus, some or all of these disclosures might be displaced as prior art by a Declaration of the co-inventors under 37 CFR 1.131.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
June 24, 2004